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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,958	04/16/2004	Robert Chalifour	50291/004002	8214

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,958	CHALIFOUR ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-53,55-69,71 and 72* is/are pending in the application.

4a) Of the above claim(s) *62-69,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-53 and 55-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claims 46, 55, 61-62 and 71-72 have been amended and claims 54 and 70 canceled as requested in the amendment filed on November 20, 2006. Following the amendment, claims 46-53, 55-69 and 71-72 are pending in the instant application.

2. Applicants' arguments in the response filed November 20, 2006 regarding the Restriction Requirement are noted. However, as the restriction has already been made final, the arguments will not be addressed.

3. Claims 62-69 and 71-72 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 27 April 2006.

4. Claims **46-53** and **55-61** are under examination in the current office action.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Rejections

6. The rejection of claims 46-51 and 56-61 under 35 U.S.C. 102(b) as being anticipated by WO 96/28471 by Findeis et al. is withdrawn in view of Applicant's amendments to the claims.

7. Applicants' argument, see in particular p. 12 of the response filed November 20, 2006, with respect to claims 46-61 have been fully considered and are persuasive. The 102(e) rejection of claims 46-53 and 55-61 as being anticipated by US Patent No. 6,743,427 B1 to Schenk as evidenced by Kalaria (*Ann N Y Acad Sci*, 1999; 893: 113-125) has been withdrawn. The rejection of claim 54 is rendered moot in view of Applicants' cancellation of said claim.

Maintained and New Claim Rejections, Necessitated by Amendment

Double Patenting

8. The provisional rejection of instant claims 46-51 over claims 1, 4, 8 and 10 of copending Application No. 10/895,646 is maintained for reasons of record set forth in the office action dated 06/16/2006 and held in abeyance until all other rejections are resolved.

9. Applicant is advised that should claim 60 be found allowable, claim 61 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both

cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

10. The rejection of claims 52, 53 and 55 under 35 U.S.C. 103(a) as being unpatentable over WO 96/28471 by Findeis et al., published 19 September 1996, in view of WO 99/27944 by Schenk, published 10 June 1999 is maintained for reasons of record and is further applied to amended claims 46-51 and 56-61 for reasons discussed below and as evidenced by Kalaria (*Ann N Y Acad Sci*, 1999; 893: 113-125). The rejection of claim 54 is rendered moot in view of Applicants' cancellation of said claim.

At page 14 of the response filed November 20, 2006, Applicants argue that the Examiner combined references describing opposing technologies in making this rejection: (i) the use of antifibrillogenic peptides binding to Aβ and inhibiting fibril formation (Findeis), and (ii) the use of peptides to induce an immune response against Aβ (Schenk). Applicants assert that because these approaches involve two totally different mechanisms, those skilled in the art would not have been motivated to combine them. Applicants thus argue that those skilled in the art would either use the peptides as antifibrillogenic agents or as vaccine antigens, but not as agents having both activities, as suggested by the Examiner.

Applicant's arguments filed have been fully considered but they are not persuasive. In response to applicant's argument that there is no suggestion to combine

the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Findeis emphasize that certain Aβ peptide sequences, in particular KLVFFA and KLVFF (which comprise SEQ ID NO: 13 (KLVF) of the instant application), are valuable for their anti-aggregation properties. Findeis recognizes that modulation of Aβ aggregation leads to a decreased neurotoxicity of the Aβ fibrils in cells in culture, and thus compounds which interfere with the production of toxic Aβ or APP fragments would be beneficial for *in vivo* treatment of amyloidosis (see column 5, lines 41-54). Findeis thus teaches that compounds having the property of binding to β-amyloid fibrils and/or modulating the aggregation of the fibrils are beneficial. Similarly, Schenk acknowledges that effective treatment and/or prophylaxis of amyloid disease means reducing the amount or level of deposited amyloid aggregates and/or inhibiting the formation of amyloid aggregates (see, for example, pp. 23-24 and Examples I and III). Therefore, in seeking a treatment for amyloid-related disease, the skilled artisan would have ample motivation to select for agents, such as Aβ peptides, that inhibit or reduce amyloid aggregation, regardless of the particular mechanism or compound employed to achieve this result.

Schenk teaches that the way to prevent or treat a disease associated with amyloid-β plaque deposits in the brain of a patient is to administer fragments of Aβ or analogs thereof to induce an immunogenic response against certain epitopes within β-amyloid. Schenk discloses that Aβ has the unusual property that it can fix and activate both classical and alternate complement cascades (see p. 14, lines 16-17). In particular, Schenk teaches, Aβ binds to Clq and C3bi, which facilitates binding to macrophages leading to activation of antibody-producing B cells. In addition, C3bi breaks down further and then binds to CR2 on B cells in a T cell dependent manner leading to a significant increase in the activation of these cells, thus eliciting the production of anti-Aβ antibodies (see p. 14, lines 18-24).

Thus, contrary to Applicants' assertion that (i) administration of antifibrillogenic peptides binding to Aβ and (ii) use of peptides to induce an immune response against Aβ are opposing technologies, the skilled artisan would recognize that administration of Aβ peptides is therapeutically useful regardless of the particular mechanism employed by the peptides to elicit the therapeutic effect. The teachings of Findeis and Schenk in particular demonstrate to the artisan that compounds which bind to and inhibit Aβ production and/or aggregation, such as anti-Aβ antibodies, are compounds capable of treating amyloid-related disease. One of skill in the art would also know that administration of a peptide with an adjuvant to a subject will generate an immune response in the form of antibodies directed to the administered immunogen, and Schenk teaches that Aβ peptide in particular will elicit an immune response and B cell activation. The antibodies generated in this response thus become the means for

achieving the desired result – in this case, inhibition of amyloid aggregation or reduction of amyloid plaque deposits. Based on the combined teachings and the general knowledge in the art regarding amyloid aggregation, the skilled artisan would further recognize that antibodies directed to a fibrillogenic portion of Aβ would be more effective to interfere with amyloid fibril formation and thus inhibit amyloid aggregation than antibodies directed to a non-fibrillogenic region of Aβ. Thus, the particular peptides disclosed by Findeis, such as KLVFFA and KLVFF, which are taught to interfere with amyloid fibril formation, would be the ideal epitope to use for the generation of anti-amyloidogenic antibodies, and the skilled artisan would be motivated to use these peptides in a vaccination method as taught by Schenk.

In addition, Schenk teaches that the immunization of PDAPP mice (a transgenic mouse model of Alzheimer's disease) with Aβ peptide fragments results in significant decreases in both total Aβ levels (a measure of both soluble and insoluble Aβ) and amyloid burden (a measure of aggregated Aβ resulting from fibrillogenesis of Aβ proteins) in the brains of the mice (see columns 44-45 and Figure 12), as well as increases in antibody titers to the immunogenic peptides (see column 46 and Figure 13), thus addressing recited limitations of instant claims 56 and 57. Schenk further teaches that these methods can be used to treat Alzheimer's disease (see column 3, lines 17-19), thus addressing limitations of instant claims 58 and 60-61. The treatment of Alzheimer's disease would encompass the treatment of cerebral amyloid angiopathy, as evidenced by Kalaria and as discussed in the previous office action (see p. 10 of the

06/16/2006 action), thus addressing instant claim 59. Accordingly, the combined teachings would render obvious instant claims 46-53 and 55-61.

11. The rejection of claims 46-53 and 55-61 under 35 U.S.C. 103(a) as being unpatentable over WO 99/27944 by Schenk, published 10 June 1999, as evidenced by Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing Inc., 1989) and Kalaria RN (*Ann N Y Acad Sci*, 1999; 893: 113-125), and in view of Tjernberg et al. (*J Biol Chem*, 1996; 271(15): 8545-8548), WO 96/28471 by Findeis et al., published 19 September 1996, Van Regenmortel et al. (*Curr Opin Biotechnology*, 1998; 9: 377-382), US 4,116,768 to Isowa et al., issued 26 September 1978, and US 6,436,903 B1 to Clayberger et al., issued 20 August 2002, filed 22 May 1996, is maintained for reasons of record. The rejection of claim 54 is rendered moot in view of Applicants' cancellation of said claim.

At pages 15-16 of the response filed November 20, 2006, Applicants argue that approaches involving inhibition of fibril formation by peptides and use of peptides as vaccine antigens involve completely different, and indeed contradictory mechanisms, and therefore the skilled artisan would not be motivated to combine these approaches. Applicants additionally argue that Schenk does not teach the claimed sequences consisting entirely of [D]-amino acids, nor do the other references cited in this rejection. Applicants thus assert that the claimed immunogenic peptides made exclusively of [D]-amino acids are an unexpected selection over the various peptide fragments suggested by Schenk and others.

Applicant's arguments have been fully considered but they are not persuasive. Applicants' arguments regarding the allegedly opposing technologies of Aβ peptides have been addressed above. In particular, the use of Aβ peptides for the treatment of amyloid-related disease is not an "either/or" problem as Applicants present it. As stated above, the skilled artisan would recognize that antibodies directed to a fibrillogenic portion of Aβ would be more effective than antibodies directed to a non-fibrillogenic region of Aβ with regard to interfering with amyloid fibril formation and subsequently inhibiting amyloid aggregation. Thus, the particular peptides disclosed by Findeis, such as KLVFFA and KLVFF, which are taught to interfere with amyloid fibril formation, would be the ideal epitope to use for the generation of anti-amyloidogenic antibodies, and the skilled artisan would be motivated to use these peptides in a vaccination method as taught by Schenk. Applicants assert that were the peptides taught by Findeis or Tjernberg to be used as vaccines, "they would stimulate the production of antibodies against them, and the antibodies would bind to the administered Aβ peptides and thus prevent their antifibrillogenic activity." While this may occur to a limited extent with each subsequent peptide immunizations, the primary target of the induced antibodies would be the fibrillogenic amino acid sequence of native Aβ protein in the body of the subject, which upon binding of the antibody to this epitope, as Applicant aptly notes, would interfere with and prevent fibril formation of Aβ in the subject, thus reducing amyloid aggregation. This is evidenced by the teachings of Schenk, demonstrating that immunization of transgenic PDAPP mice with Aβ peptides lead to a significant decrease in amyloid deposition in the brains of the animals which was correlated with a significant

increase in anti-Aβ antibody titers. If the antibodies generated in the vaccination method were exclusively and/or predominantly binding to the administered Aβ peptides, there would be no observed reduction in amyloid burden. However, since Schenk demonstrates that brain amyloid burden is actually reduced upon Aβ peptide immunization, the skilled artisan would recognize that the antibodies are effecting the desired therapeutic result and not interfering with the peptide vaccine.

In response to Applicants' second argument – that none of the references teach peptides made exclusively of [D]-amino acids – the Examiner notes that such teachings were addressed by Findeis, who discloses that anti-fibrillogenic peptides of the invention, such as the Aβ peptide sequences KLVFFA and KLVFF (which are identical to instantly claimed SEQ ID NOS: 7 and 15, and which would also comprise SEQ ID NO: 13 (KLVF) of the instant application), may be modified by substitution of all D-amino acids for all L-amino acids within the compound (p. 17, lines 18-20) (see also p. 17 of the previous office action). Accordingly, claims 46-53 and 55-61 remain rejected as being obvious to the artisan at the time of filing in view of cumulative reference teachings.

Conclusion

12. No claims are allowed.

13. This application contains claims drawn to an invention nonelected with traverse in the response filed April 27, 2006. A complete reply to the final rejection must include

cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Kimberly Ballard, Ph.D.
February 8, 2007